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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/527,830

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Toshimitsu Nakashima

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EXAMINER

WALICKA, MALGORZATA A

ART UNIT

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1652

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/527,830	Applicant(s) NAKASHIMA ET AL.	
	Examiner MALGORZATA A. WALICKA	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 2 and 9-14 is/are withdrawn from consideration.
- 5) ☒ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/13/05 and 7/5/06</u> . | 6) <input type="checkbox"/> Other: _____ |

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The application is the national stage application of PCT/JP03/013022. Preliminary amendment to the specification, abstract and claims was filed together with the application on March 14, 2005. Claims 4-8 were amended and claims 9-14 were added. Applicants elected group I, claims 1 and 3-8 without traverse, and these claims are under examination. Claims 2 and 9-14 are withdrawn from examiner's consideration as directed nonelected invention.

DETAILED ACTION

Priority

Applicant's claim of the benefit of priority to the Japanese application 2002-297601, filed Oct. 10, 2002 has been noted. Priority of the claims under examination to the Japanese patent has been granted.

Specification

The specification contains typographical errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

Objections

The examiner suggests the following changes to the language of the preamble of claim 1: "a method of producing copolyester by a culture of a microorganism".

Rejections

35 USC 112 second

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3, lines 3-4, recites the limitations: "the composition", "selecting the species" and "the control value". There is insufficient antecedent basis for these limitations in –claim 1, -

35 USC 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is - directed to a method of producing a copolyester by a culture of a microorganism wherein the method comprises controlling a specific substrate feed rate

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of an oil or fat to be used as a carbon source at a constant value throughout the whole culture period. -Claims 3-8 add further limitations to claim 1, wherein the method comprises controlling composition of the polyester by selecting specific substrates by using a control value (claim 3); wherein oil or fat used as a carbon source is selected from a group consisting of soybean oil, corn oil, etc. (claim 4); wherein the oil or fat used as a carbon source contain lauric acid in the constituent fatty acids (claim 5); wherein the microorganism is selected from the group consisting of microorganisms belong to the genus *Ralstonia*, the genus *Pseudomonas*, the genus *Aeromonas*, the genus *Alcaligenes* and the genus *Escherichia* (claim 6); wherein the microorganism is a transformed microorganism into which a polyester polymerase gene is incorporated (claim 7); and wherein the copolyester contains 3-hydroxyhexanoic acid unit (claim 8).

The claims are generic and lacking sufficient written description of:

- 1) any copolyester,
- 2) any microorganism,
- 3) any oil or fat,
- 4) any constant value of a specific substrate feed rate and its control value, and
- 5) any polyester polymerase.

Neither the claims nor the specification define the terms polyester and copolyester. Applicants present a method of producing biodegradable polyester of the general formula $P(HB-co-3HH)$ wherein the 3HH content is possibly high. This is the only one species of the genus polyesters including copolyesters. Polyesters are an extremely large and versatile family of the chemical compounds, therefore $P(HB-co-$

3HH) species does not identify the genus as a whole. In the PTO 892 form the examiner provides results of search for the terms polyester and copolyester in Wikipedia published on the Internet. The items "polyester" and "copolyester" as presented in the Wikipedia even do not mention the polymer P(3HB-co-HH) which applicants synthesized. Thus, the structure of the products to be produced by the claimed method is not described by the terms polyester/copolyester. Furthermore, applicants have shown that the relative content of 3HH and 3HB in the copolyesters they synthesized depends on the culture condition, i.e., the structure of the carbon source such as oil or fat and the rate under which the substrates are provided to the culture. The lower specific substrate rate favors higher content of 3HH. The claims, however, do not state any numerical value of the % of 3HH in the copolymer obtained by the claimed method. In addition the limitation of claim 1 "a constant value [of the specific substrate feed rate] throughout the whole culture period" is not describing what applicants did. Judging from Figs 1 and 2, the constant value of the specific feed rate of the carbon source took place only during 36-70 h of culture, not in a seed culture and at the beginning of fermentive culture. Thus, the claims do not described what applicants did.

Furthermore, any percentage of 3HH content in the copolymer strictly depends on conditions of the culture which are absent from the claimed limitations. The percentage values of 3HH quoted in the tables in Example 1 are result of particular conditions of culture. In addition, Applicants used for their experiments only one microorganism, which is *Alcaligenes eutrophus* AC32 that contains polyhydroxyalkanoic acid synthase of *A. caviae*; page 3 of the specification. This engineered microorganism

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provides for a relatively high content of 3HH in the produced copolyester. Other microorganism broadly incorporated in the scope of claim 6 are not necessary a suitable producers of P(3HB-co 3HH); at least the disclosure fails to present any data to this effect. Therefore, the carbon source (specific oil and fat), the specific feeding rate, the microorganism species used for culture and the specific synthase that is expressed in the host cell used for culture determine the 3HH content of the product synthesized i.e. the structure of the product. The extremely broad scope of the claims causes that one having skills in the art is not convinced that at the time of filing the application Applicants were in possession of the claimed invention.

Scope of enablement

Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of production copolyester P(3HB-co - 3HH) containing percentage of 3HH as quoted in the tables of the Examples, using *Alcaligenes eutrophus* AC 32, transformed with polyhydroxyalkanoic acid synthase of *A. caviae*, wherein the conditions of culture are that described in the tables presented in the Examples does not reasonably provide enablement for production of

- 1) any copolyester,
- 2) using any microorganism, including that transformed with any polyester polymerase or being those recited by claim 6,
- 3) using as a carbon source any oil or fat, and
- 4) any constant value of a specific substrate feed rate.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any method of producing any copolyesters by a culture of any microorganisms, wherein the specific substrate rate has any constant value throughout the whole culture period. The state of art of fermentative production of copolyesters depends on the structure of copolyesters at hand including the biodegradable polymer P(3HB-co-3HH) which is a main embodiment of applicants' invention. Providing a specific example of production of P(3HB-co-3HH) containing percentages of 3HH quoted in the tables of the Examples, using *Alcaligenes eutrophus* AC 32 transformed with polyhydroxyalkanoic acid synthase of *A. caviae*, wherein the conditions of culture are that described in the tables, does not

reasonably provide sufficient guidance on production of any copolyester of an extremely large genus of all copolyesters currently known and to be disclosed. Applicants provision for a general structure of P(3HB-co-3HH) does not provide a guidance neither for chemical structure of any copolyester nor for any variations within the structure P(3HB-co-3HH) itself. Furthermore, as to the constant specific feed rate of carbon source instructions given in the tables do not provide a sufficient guidance for any specific feed rate of any oil and fat as required by the claims. Moreover, cultivation of *Alcaligenes eutrophus* AC 32 under conditions described in the Examples does not necessary provide instruction suitable for any microorganisms broadly used in the claimed method or even for microorganisms of claim 6. In addition, the microorganisms recited by claim 6 differ in their requirements for the carbon source and culture conditions for production a specific polyester having a definite structure and the scope of the claims covers any copolyesters one may think of. Claim 13, recites any polyester polymerase gene, but applicants provide an instruction only for polyhydroxyalkanoic acid synthase of *A. caviae*. Even if one skilled in the art would limit the enzymes to polyhydroxyalkanoic acid synthase, these enzymes are not known for many organisms and the scope of the claim comprising any polyester polymerase gene has no reasonable enablement in the disclosure.

In conclusion, the claims suffer from lack of guidance as to the structure of the polyester to be synthesized, the microorganism useful for synthesis, specific carbon sources and specific substrate feed rates of said sources, as well as polyester synthases that are to be used for transformation of said microorganisms.

In summary, because the claimed method depends on a subtle interplay of so many elements for which the disclosure does not provide a sufficient guidance, a skilled artisan who would like to make and use the claimed invention is forced to experimentation that has a low probability of success and is undue.

35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

A. Claim 1, 3-4 and 6-8, Patent rejected under 35 U.S.C. 102(a) as being anticipated by JP2001340078, publication date 2001-12-11; enclosed in IDS.

Claim 1 is - directed to a method of producing a copolyester by a culture of a microorganism wherein the method comprises controlling a specific substrate feed rate of an oil or fat to be used as a carbon source at a constant value throughout the whole culture period. Claims 3-8 add further limitations to claim 1, wherein the method comprises controlling composition of the polyester by selecting specific substrates by using a control value (claim 3); wherein oil or fat used as a carbon source is selected from a group consisting of soybean oil, corn oil, etc. (claim 4); wherein the microorganism is selected from the group consisting of microorganisms belong to the genus *Ralstonia*, the genus *Pseudomonas*, the genus *Aeromonas*, the genus

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Alcaligenes and the genus Escherichia (claim 6); wherein the microorganism is a transformed microorganism into which a polyester polymerase gene is incorporated (claim 7); and wherein the copolyester contains 3-hydroxyhexanoic acid unit (claim 8).

The Japanese Patent describes a process for producing polyester comprising 3HB and 3HH using Alcaligenes eutrophus (Ralstonia eutropha). It also describes controlling the molar ratio of 3HH by altering the amount of added oil/fat or fatty acid that is used as a carbon source, the use of coconut oil; palm oil, and palm kernel oil as the oil/fat, a composition of fatty acid comprising 47 % lauric acid as a carbon source, the use of microorganisms transformed by a recombination vector that contains the gene of a polyester polymerizing enzyme isolated from Aeromonas caviae. It also states that if the oil/fat is added in a large amount at one time, the concentration of dissolved enzyme in the culture liquid may be decreased and because fatty acids are cytotoxic they may inhibit growth. Therefore, a method in which the fatty acid is added in divided amounts such that they do not inhibit growth or a method in which they are added continuously to maintain a concentration that does not inhibit growth is preferred.

The patent anticipates all details of the claimed invention and is published 11 months earlier than the filing of PCT application of which the constant application is a national phase.

35 USC 103

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP2001340078, publication date 2001-12-11; enclosed in IDS as applied to claims above, and further in view of Chen G. Q et al., Industrial scale production of poly(3-hydroxybutyrate-co 3-hydroxyhexanoate), App. Microbiol. Biotech, 2001, 57, 50-55, publicly available July 26, 2001; encompassed in IDS.

Claim 5 is directed to a method of producing a copolyester by a culture of a microorganism wherein the method comprises controlling a specific substrate feed rate of an oil or fat to be used as a carbon source at a constant value throughout the whole culture period, wherein the carbon source contains lauric acid in the constituent fatty acid and the culture is carried out under the condition that phosphorus is being restricted.

The Japanese Patent, as discussed in the above rejection under 102(a), describes a process for producing polyester comprising 3HB and 3HH using *Alcaligenes eutrophus* (*Ralstonia eutropha*). It also describes controlling the molar ratio of 3HH by altering the amount of added oil/fat or fatty acid that is used as a carbon source. The document teaches the use of a **fatty acid comprising 47 % lauric acid** as a carbon

source. It also states that if the oil/fat is added to the medium in high quantities it is toxic. Therefore, a method in which the fatty acid is added in divided amounts such that they do not inhibit growth or a method in which they are added continuously to maintain a concentration that does not inhibit growth is preferred.

The Japanese patent, however does not describe the conditions that the phosphorus content in the medium is restricted.

Chen et al. teach in the abstract the synthesis of P(3HB-co-3HHx) in a culture of *Aeromonas hydrophilia* was triggered by addition of lauric acid under limited nitrogen or phosphorus. On page 52, right column, line 6, they teach that limiting phosphorus content was 2.3. times more efficient for production of the polymer than limiting nitrogen. Therefore, they further cultivated the microorganism for the production P(3HB-co-3HHx) under lauric acid and phosphorus content limitation.

It would have been obvious to one having ordinary skills in the art at the time of invention who would like to produce P(3HB-co-3HH) to use the method of P(3HB-co-3HH), i.e., production disclosed by the Japanese patent and limit the phosphorus content in the medium in order to increase the polymer production as Chen et al. did.

The motivation of combination of the teachings of the patent and Chen would be to improve efficiency of production of P(3HB-co-3HA); a polyester that is industrially and environmentally attractive as biodegradable. The expectation of success was very high because both documents provide for a very efficient production of P(3HB-co-3HH). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

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CONCLUSION

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached on (571) 272-0934 -. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner,

/Tekchand Saidha/

Primary Examiner, Art Unit 1652

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